IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Taylor et al.
Serial No:	10/766,599
Filing Date:	01/27/2004
Title:	NOISE REDUCTION FOR SPECTROSCOPIC PROCESSING
Examiner:	Daniel R. Sellers
Art Unit:	2644
Confirmation No.:	3408

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Date: *February 11, 2008*

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DECLARATION OF HOWARD S. TAYLOR

I, HOWARD S. TAYLOR, declare as follows:

1.   I am an Emeritus Professor of Chemistry and Physics at the University of Southern California. For many years, I have been extensively involved in research and teaching in a number of fields, including but not limited to: atomic and molecular spectroscopy, and mathematical methods of signal processing. I have written and spoken extensively in these fields for many years, and I am considered an expert in these fields. I am an elected Fellow of the American Physical Society and the American Association for The Advancement of Science. In 1992 I was awarded by the German Ministry of Science and Education the Max Planck Award for Atomic and Molecular Physics. My research has been supported from1961 to 2006,when I retired, by either or both of the National Science Foundation and the Department of Energy.

2.   I am also one of the co-inventors on the above-identified patent application
No. 10/766,599 ("the '599 application") and am familiar with its prosecution history.

3.   In particular, I have read the statements made by the Examiner in the final
Office Action mailed Sept. 11, 2007 (the "Office Action"), with respect to the claims
at issue being rejected under 35 U.S.C. §§ 102 and 103, as allegedly being
rendered unpatentable by certain prior art references.

4.   I have also reviewed in detail the following prior art references, cited in the
final Office Action as a basis for the rejection of the claims at issue: U.S. Pat. No.
5,420,508 to Smith et al. ("Smith"); U.S. Pat. No. 5,148,379 to Konno ("Konno");
and U.S. Pat. No. 3,752,081 to Freeman ("Freeman").

5.   The following background about the inventive concepts in the '599
application is provided, in order to help the Examiner, as well as any other reader
of the '599 application, appreciate the novelty and originality of the '599
application.

6.   In general, during a basic NMR (Nuclear Magnetic Resonance) experiment, a
series of time signals (often called "transients" in the art) are continuously collected
until the operator gives a "stop" command. Very roughly speaking, these transients
indicate a response of the nuclei (within the sample being tested) to an external
magnetic field, and contain information relating to the molecular structure and
other properties of that sample.

7.   After certain fixed (predetermined) times in the collection process all
transients that have been previously collected are averaged to reduce noise, and
this averaged signal is Fourier transformed[1] into a spectrum[2] which then is

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[1] A Fourier transform is a well known process that is widely used for all types of signals. A Fourier transform
converts a signal that is a function of time into a signal that is a function of frequency.
[2] A "spectrum" shows the magnitude of each Fourier-transformed signal, as a function of frequency.

exhibited to the user or operator. The operator essentially sees a movie that proceeds on the time scale of transient collection.

8.   At any point in this collection, the operator can end the experiment by choosing to stop collecting further transients, and walk away with the final transient-averaged signal and its Fourier transform (i.e. the spectrum).

9.   The conventional criterion for "stopping", or equivalently not asking for more transients, is either the opinion of the operator as to the acceptability of the signal-to-noise ratio of the spectrum that was so far obtained from the averaged signal, or the empirical fact that no signal is observable above the noise in a practical amount of collection time. Because of the frequent occurrence of the latter criterion, NMR experiments are not even attempted for the purpose of collecting spectra from nuclei which have very low natural abundances.[3] A time consuming chemical re-synthesis using commercially expensive isotope enriched precursor reagents is needed to obtain a compound from which one can then obtain satisfactory NMR spectra.

10.   Recent publications authored by the Applicants of the '599 application ("Applicants"), based on the methodology of the '599 application, have taught a new signal collection and signal processing method (and associated software system) that can _greatly_ reduce the number of transients needed to observe an acceptable NMR spectrum and can thus make it possible to carry out the above NMR experiments without having to perform isotope enrichment in most cases. This new method and system, which is disclosed and claimed in the '599 application, can also be advantageously used to reduce machine time in many NMR experiments.

11.   The key original idea[4] in the '599 application is to replace the above mentioned prior art criteria for "stopping" the collection of transients by a new

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[3] By way of example, Nitrogen 15, Oxygen 18, Carbon 13.
[4] Set forth e.g. in claim 1 part c), and claim 15.

criterion which does <u>not</u> involve observing a "movie" of an evolving Fourier spectrum, as in conventional methods, but instead involves observing a "movie" of the evolving <u>plot of the singular values</u>[5] shown in order of decreasing magnitude. At any point in the collection of transients the singular values are obtained using well established methods from the same average-over-transients signal used in the conventional art. In the '599 application, the criterion that is adopted for stopping the collection of transients is the <u>appearance of a stable gap</u> in the plot of singular values.

12.   To best of my knowledge, such a method and system for collecting and processing NMR signals has never been known or used before by anyone else.

13.   The above-mentioned plot or graph of singular values is familiar from the singular value decomposition (SVD) method, well known in the art. The SVD method is routinely used by all types of signal processors, in order to create a signal with greatly reduced noise. The software then transforms the signal into a spectrum.

14.   In one embodiment of the '599 application, Harmonic inversion (also well known in the art) is used to create the desired spectrum as it produces a better resolved spectrum than a Fourier transform for given number of samples in the time series transient and requires no more computing time than the Fourier transform.

15.   In the '599 application, the characteristic of the singular value graph that tells the user (who generally starts with a very noisy signal), that it is time to stop collecting transients is the observation by the user that a finite fixed number (call it K) of the higher singular values have roughly stopped decreasing in value with respect to further transient collection. The remaining singular values keep on descending in magnitude when further transients are collected. This creates a

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[5] As set forth in the '599 application, these singular values are the positive eigenvalues of a correlation matrix constructed from the individual samples that form the time averaged signal.

visible gap in the locus of the singular values SV_i (i = 1, ..., N), when these singular values SV_i are plotted against their index i. In the '599 application, it is the appearance of this gap, not the actual magnitudes or values of the singular values, that tells the user or operator to stop collecting transients. This, in a nutshell, is the novelty disclosed and claimed in the '599 application.

16.   Such a visible gap in the plot of singular values occurs when the signal to noise ratio is about 1.1, a value at which the signal peaks in prior art are not seen and which in prior art methods requires many[6] times more transients in order to get an acceptable spectrum by Fourier techniques.

17.   Conventional prior art SVD-plus-harmonic inversion applications have been used very infrequently for reasons given below in an " after experiment-off machine" mode without using the above-described novel feature of the '599 application. In these prior art methods, the SVD method plus harmonic inversion was often used to analyze experiments that did not have enough collected transients and which therefore gave unsatisfying results. Such cases simply used the last available averaged signal. If a sufficient number of transients had been by chance collected so that the signal-to noise ratio was greater than 1.1, a gap was therefore seen, and a true spectrum was obtained.

18.   This latter method was never applied in challenging experiments because of the problem of needing to collect a large number of transients without any guarantee of seeing a gap. Then to possibly locate the elusive gap one had to re-do the whole experiment, wasting the previous results again with no guarantees of seeing the gap. A method of finding the gap, as disclosed and claimed in the '599 application, was needed. Such a method would ensure that nothing would be wasted. Such a method was not known or used until Applicants disclosed it in the '599 application. Instead, those who carried out the signal processing accepted

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[6] Generally of the order of a factor of four to twenty five.

signals by experimentalists who had no idea of what was to be done during the processing of signals.

19.   When the processor didn't see a gap the number K was either estimated intuitively, taken without comment to be the size of matrices made from the data or was computed by mathematical methods which turned out to be unreliable. A too small K missed true peaks and a too large one gave extra false peaks. The false peaks in harmonic inversion theory can be shown to be due to noise. False peaks are "unforgivable" in our scientific culture and is the reason these non-linear methods are rarely used and had a very bad reputation. Not realizing or not using the fact that a stable gap in a plot of singular values gave the correct K and that this gap could and should be used as a reliable, theoretically rigorous and accurate criterion for defining the necessary amount of transient collection was the cause of these errors.

20.   Simply put, one cannot get a reliable spectrum without knowing K and to the best of my knowledge, a search for the gap, as set forth in the '599 application, is the only practical way to determine it.

21.   The methods and systems disclosed and claimed in the '599 application integrates the finding of the gap into the experimental process, admits defeat when the allotted machine time doesn't allow the gap to be revealed and stops collecting when commanded to do so, in a much shorter time compared to what the present art needs to produce an acceptable Fourier based spectrum. In the vast majority of cases, the methods and systems disclosed and claimed in the '599 application require an amazingly fewer number of transients in order to see and obtain the spectrum, compared to the number of transients commonly required in the present art. The method can be used to "speed up" all transient collections, a feature which can be of immense value in laboratories, hospitals, and other organizations that perform NMR experiments.

22.   On information and belief, the Examiner was not cognizant of the above teachings of the '599 application. He compared the methods and systems claimed in the '599 application to patents and documents and combinations thereof which, while using one or more of the well known mathematical methods (such as SVD[7] and harmonic inversion) that are also used in the '599 application, did not teach, suggest, or disclose in any way any of the the above-described novel features of our invention in the '599 application. These patents and other documents had absolutely nothing to do with the problem I lay out above, namely finding a reliable criterion for stopping transient (or signal) collection in order to acquire meaningful NMR spectra in an acceptable amount of machine time.

23.   Turning now to the first reference used by the Examiner to reject the claims of the present application, Smith describes[8] the conventional use an NMR apparatus to collect many transients, and to average them to reduce noise in the final averaged time signal. For various reasons, the final averaged time signal is called an FID (Free Induction Decay) in the art. In Smith, it is described that if the numerical analysis is not numerically stable by criteria unique to the problem at hand, one comes back and collects more transients, to further reduce noise in the hope of getting better results. Such a data collection cycle is well known and part of every NMR experiment, and the software for this is typically provided by the manufacturer in any newly manufactured NMR machine.

24.   The rest of what is disclosed in Smith has nothing in common with the '599 application. For example, <u>Smith does not teach or suggest converting signals into a spectrum</u>. In fact, Smith does not even look at any spectrum. In contrast, in the '599 application the final product is the spectrum, as explicitly described and stated in the '599 application, and as explained above.

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[7] Singular Value Decomposition
[8] <u>See e.g.</u> Col 3, 31-34; Col 5, lines 57-62 of Smith.

25.   Smith attempts to develop empirical polynomial expansions[9], between macroscopic properties (such as density, melt indices etc.; these properties are called "Y" in Smith) of oils and fats and a set of variables that Smith calls "X". In order to obtain values of the X, Smith expands the time dependent FIDs in a linear sum of various time functions (which are misleadingly termed "equations" in Smith). The time functions vary from problem to problem and may be Gaussian, or trigonometric, or exponential functions, by way of example.

26.   To get the coefficients of the functions in the expansion, Smith uses the well known M-L version of the least squared method,[10] employing a Chi-squared difference between the FID and the expansion. The X are the amplitudes (i.e. maximum height) of each term[11] in the time function expansion. The X must be guessed and used to start the M-L process. During the M-L process, it is "discovered" in Smith (col. 3; line 59) that there are instabilities and that it is very difficult to converge the least squares process. Such a "discovery" is simply the very well known fact that instabilities arise when a process is used where there is more data (the time samples of the FID) than unknowns (the expansion coefficients).

27.   In Smith, repeated runs with the same FID give different results. On information and belief, the Applicant in the Smith patent does not realize that this is because the rank of the data matrix is less than its dimension. In high school, one would have said the rows of the matrix are linearly dependent, and then one would have used row operations to zero out as many rows as one can. These zero rows would cause the determinant of the matrices (which in Smith are made from the initial guesses, and which need to be inverted in the M-L procedure) to equal zero, and its inverse (needed to solve for the unknown coefficients) to become infinite.

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[9] These empirical polynomial expansions are referred to as a "model."
[10] While the M-L version of the least squared method is well known, it is NOT used in the '599 application and is irrelevant to the '599 application.
[11] Each term is one coefficient arising from the fitting, times one time function

In numerical processes, this means that the solutions[12] are unstable, and thus change with trivial changes of input.

28.   To alleviate this problem, Smith uses the principle component analysis (PCA), which is equivalent to SVD, to find linear independent vectors (referred to as "Z" in Smith). The number of these vectors Z is called K in Smith, and is obtained from the number of "not so small" eigenvalues. The eigenvectors associated with these larger eigenvalues become the rows of a new input matrix with which Smith starts the M-L procedure again. Smith then needs a convergence criterion. Comparing all the large number of new X variables is impractical. Therefore, he uses the repeated appearance of the smallest eigenvalue to be within a few standard deviations of what Smith calls "calibration" value is as a criterion to go on. Smith then uses regression analysis, fitting the "Y" to a polynomial in the "X". Such a fitting process would have led to incorrect results if Smith had used unstable and/or multivariate variables.

29.   In paragraph 2 of the final Office Action, spanning pages 2–4 of the Office Action, the Examiner makes a number of incorrect statements. In Smith the SVD or PCA procedure is not done to separate noise from signal, in contrast to the present application. In the problem faced by Smith there is no theoretical basis for such a separation. This is in contrast to the present application in which a theoretical basis for claiming such a separation is provided by the theory of NMR. In Smith, PCA is carried out so as to solve the multivariate (linear dependence) problem, NOT to remove or reduce noise from signals that contain desired information.

30.   Smith cannot and does not associate any specific singular values with noise. Contrary to the Examiner's comments, there is nothing whatsoever in the teachings of Smith that in any way suggests or relates to noisefree singular values or noise associated singular values, let alone any gap between them. In fact, Smith never

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[12] I.e., the values of the "X," and vectors made of the "X". These vectors are rows of the matrix to which PCA will be applied.

uses the word noise in discussing the mathematical procedures. Any association of noise with the mathematical procedures discussed in Smith is false and non-existent.

31.   In Smith, when the search for independent variables can't converge, it is correctly assumed that the problem is almost certainly in the quality of the FID (i.e. the final averaged signal), and noise is reduced[13] by collecting more transients, as does practically everybody else when the signal-to-noise ratio is not satisfactory.

32.   The Examiner points out that Smith makes a vector space problem out of the "X." In the '599 application (dealing with NMR signals) one creates a vector space directly out of the data samples in the averaged signal. Creating a vector space is a routine mathematical tool taught in practically all modern mathematical books. Neither the '599 application nor Smith has any claim on the originality of creating vector spaces. Rejecting the claims of the '599 application because they recite creating vector spaces is akin to rejecting the claims because they recite using calculus.

33.   The problem discussed in Smith is so totally different from the problem treated by the '599 application that any attempt at comparing the two is simply comparing "apples to oranges". The only thing the '599 application has in common with Smith is that the '599 application uses the SVD / PCA method. But the SVD / PCA method is used in many textbooks and in an enormous variety of applications, and SVD/PCA is definitely not what is claimed as the novel inventive feature(s) in the '599 application. Specifically, Smith does not, in any form or shape, teach or suggest or mention identifying a gap between a noisefree singular value and a noise singular value, in a graph of the singular values, as a criterion for determining whether a sufficient number of measurements ("transients" in NMR) have been made and therefore no further measurements are needed.

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[13] See e.g. Fig. 3 in Smith.

34.   Turning to Konno, which is another reference cited by the Examiner, Konno is also completely unrelated to the subject matter of any of the claims of the present application. First, the material in Konno has nothing to do with NMR spectral acquisition. Konno is not even an analysis of any experiment, nor is Konno involved in signal processing. By any reasonable standards, comparing the '599 application with Konno is like comparing apples to oranges.

35.   The mathematics used in Konno has no relation to the mathematics used in the '599 application. The matrices in Konno come from discretization of differential equations. The only correspondence between Konno and the '599 application is in the use of similar words[14] that arise in mathematics. Konno uses the constancy of the eigenvalues of a matrix produced in Konno's simulations to test if his simulations give stable results. The Examiner mistakenly calls the eigenvalues in Konno singular values. But the eigenvalues in Konno are not singular values. In the '599 application, the singular values are produced by a method that makes the singular values appear as eigenvalues of a correlation matrix; the singular values could have been produced another way in which they would not be eigenvalues.[15]

36.   Konno does not use SVD. Konno doesn't perform signal processing. Konno doesn't even have an experiment or measurement noise. Again, the Examiner claims as previous teachings things that are familiar words appearing in common mathematics textbooks, and which are used both by Konno and the '599 application. If one GOOGLEs these words, the work described and claimed in the '599 application, Konno's work, and a million other works might show up. This is the sole connection between Konno and the '599 application.

37.   The novel features recited in the claims of the '599 application, or even any parts of these novel features, do not appear anywhere in Konno. Absolutely nowhere does Konno teach or suggest or mention, in any form or shape, the identifying of a gap between a noisefree singular value and a noise singular value,

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[14] Not even the phrases are the same.
[15] Eigenvalues are taught in most advanced college math classes.

in a graph of the singular values, as a criterion for determining whether a sufficient number of measurements ("transients" in NMR) have been made and therefore no further measurements are needed.

38.   Regarding Freeman, also cited by the Examiner, Freeman deals with NMR measurements, as do a great many people every day. The fact that NMR measurements are involved is the only thing Freeman has in common with the '599 application. Freeman is not about reducing noise in the NMR data collection as is the '599 application. Freeman teaches how to perform a non-standard experiment to obtain spin-spin coupling constants. Freeman uses standard Fourier methods to analyze a collected signal that is of a different type than the signals disclosed and claimed in the '599 application. Freeman does not have any thing new to say about data collection and reducing noise which is the subject matter of the '599 application. On information and belief, Freeman does not claim to do so because data collection and reducing noise is not the purpose in Freeman.

39.   It goes without saying that nowhere does Freeman teach or suggest identifying a gap between a noisefree singular value and a noise singular value, in a graph of the singular values, in order to determine whether a sufficient number of measurements (of a sample to external excitation) have been made.

40.   For all of the reasons set forth below, neither Smith, or Konno, or Freeman, either alone or in combination, teaches or suggests the subject matter of the rejected claims. In particular, the following claims at issue are neither taught or suggested by either Smith, or Konno, or Freeman, or any combination thereof: Claim 1 (specifically, parts b and c of claim 1); all claims depending[16] on claim 1; claims 14-17; and claims 25-28.

41.   I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

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[16] Currently pending claims that depend on claim 1 are: claims 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, and 13.

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing there from.

Respectfully submitted,

Howard S. Taylor, Ph. D.

Signed this 11th day of February, 2008